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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,967	11/03/2003	Heiner Glombik	DEAV20010041USCNT	5028

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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 06/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/699,967	GLOMBIK ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *10-15,18 and 19* is/are allowed.

6)☒ Claim(s) *9, 16, 17, 20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/25/2005
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 3/10/2005 has been received, entered and carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 1-8 have been canceled.

2. Claims 9-10, 12, 14, 16, 18, 20 and 21 have been amended.

3. Remarks drawn to objections to claims, specification and rejections under 35 USC 112, second paragraph, double patenting and 103(a)

Claims 9-21 are pending in the case.

The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

Claim Objections

The objections to claims 4 and 6 have been rendered moot by cancellation of the claims. Claim 9 is objected to because of the following informalities. Claim 9 does not recite the proper Markush language "selected from the group consisting of". Appropriate correction is required.

Specification

The objections to the specification have been overcome by amendments.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 16-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating cholesterol reduction, does not reasonably provide enablement for the treatment and prophylaxis of any physiological function. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

(A) The breadth of the claims

(B) The state of the prior art

© The level of one of ordinary skill

(D) The level of predictability in the art

(E) The amount of direction provided by the inventor

(F) The existence of working examples

(G) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

Claim 16 is drawn to a method of effecting the prophylaxis or treatment of a physiological condition comprising administering a pharmaceutically effective amount of

the composition of matter according to Claim 9. The claim is seen to encompass any condition.

The state of the prior art

The examiner notes that prior art US 622187 mentions methods for lowering cholesterol levels. However, there is no disclosure of a method of effecting the prophylaxis or treatment of any condition.

The level of one of ordinary skill

The skilled artisan in this field is that of an MD/Ph.D.

The level of predictability in the art

Based on the disclosure in the prior art the Examiner notes that prophylaxis and treatment of any physiological condition is highly unpredictable. There is not seen sufficient data to substantiate the assertion that any physiological condition can be treated or prevented.

The amount of direction provided by the inventor

The instant specification is not seen to provide enough guidance that would allow a skilled artisan to extrapolate from the disclosure and the examples provided to enable the use of the active agents for the prophylaxis and treatment of any physiological condition. The specification also fails to direct the skilled artisan in correlative prior art procedures which might provide the basis for such a treatment.

The existence of working examples

The working examples set forth in the instant specification are drawn to data involving lipid and cholesterol levels in hamsters. The skilled artisan in this field would not extrapolate the efficacy of the compounds claimed or the use of the same in the prophylaxis and treatment any physiological condition from just this example provided. The disclosure does not show the prophylaxis and treatment of any physiological condition. However, it is seen to show the effect of the active agents in lowering cholesterol.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Indeed, in view of the information set forth, the instant disclosure is not seen to be sufficient to enable the prophylaxis and treatment of any physiological condition with the compounds set forth in the claims. A skilled artisan would have to perform additional experimentation inorder to determine the amount of the active agents, the frequency of administration, etc., based on the condition being treated.

The rejection of claims 1, 3-6, 11, 13, 15 and 20under 35 USC 112, second paragraph have been overcome by amendments and explanations provided by the applicants.

The rejection of claims 9-2 is being maintained for reasons of record.

Applicants have provided a document in support of the use of the trademark Caromax in claim 9 and a reference to page 9 of the specification for a description. This does not overcome the rejection. Even though the specification describes the said term, the limitations from the description in the specification cannot be read into the claim. The ingredients of Caromax should be recited in the claim and the term Caromax should be deleted. Claim 9 has been amended to recite the terms "physiologically functional derivatives". In the absence of the specific derivatizations to the chemical core claimed or distinct language to describe the structural modifications or the chemical names of the derivatives of this invention, the identity of said derivatives would be difficult to describe and the metes and bounds of the said derivatives applicants regard as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated. Applicants have pointed out to the definition of the said terms at page 3 of the specification (for the use of the said terms in claim 1, which is now cancelled). The specification defines the terms as any physiologically tolerated derivative of the compound of the invention, e.g., a prodrug such as an ester or an active metabolite thereof. This does not overcome the rejection. First of all, definitions in the specification cannot be read into the claims even though claims are interpreted in light of the specification. If applicants intend a prodrug or a metabolite then those specific prodrugs or metabolites have to be recited in the claims. It is not possible to assess the metes and bounds of the terms prodrug and active metabolites.

The rejection of claim 16 is being maintained for reasons of record. It is not clear what condition is being treated.

Claims that depend from rejected base claims that are unclear/indefinite are also rendered unclear/indefinite and are rejected for the same reasons.

Double Patenting

The obviousness-type double patenting rejection of instant claims 1-7 as being unpatentable over claims 5-6 of US Patent No. 6,387,944 has been rendered moot by cancellation of instant claims 1-7. The obviousness-type double patenting rejection of instant claim 20 as being unpatentable over claims 5 of US Patent No. 6,387,944 ('944 patent) is being maintained for reasons of record.

Instant claim 20 recites the open-ended language comprising which means that the said instant composition can contain other ingredients including the compounds of formula 1. Since claim 5 of the '944 patent is also drawn to a composition comprising compounds of formula 1, which happens to substantially overlap with the compounds of instant formula 1, the compositions of instant claim 20 and that recited in claim 5 of the '944 patent are seen to overlap.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 21 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,387,944 ('944 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claim 21 is drawn to a process of producing a pharmaceutical composition comprising the composition of matter of claim 9, comprising mixing the compound of formula I and the other active ingredient with a pharmaceutically carrier and converting the mixture into a suitable form for administration.

A similar process limitation is seen in claim 8 of the '944 patent that comprises mixing of compounds that are recited in formula (I) of instant claim 21 with excipients.

It would be obvious to one of ordinary skill in the art that the process of the instant claim 21 and the process of claim 8 in the '944 patent are substantially overlapping since both processes involve mixing the respective ingredients to make the composition and one of ordinary skill in the art would be motivated to use the same process for this reason. Making a composition by mixing various active ingredients can be accomplished with a reasonable amount of success. The process of the instant application should recite limitations that are patentably distinct over those of the '944 patent.

The obviousness-type double patenting rejection of instant claims 1-7 as being unpatentable over claims 19-20 of US Patent No. 6,221,897 has been rendered moot by cancellation of instant claims 1-7. The obviousness-type double patenting rejection of instant claim 20 as being unpatentable over claim 19 of US Patent No. 6,221,897 ('897 patent) is being maintained for reasons of record.

Instant claim 20 is drawn to a pharmaceutical composition comprising a carrier, the compound of formula I and the other active ingredient according to claim 9. Since the claim recites the open-ended language comprising, the said composition can comprise additional ingredients. Claim 19 of the '897 patent is also drawn to a composition comprising compounds of formula 1, which happens to substantially overlap with the compounds of instant formula 1 and also comprises an excipient. A clear-cut distinction between a carrier and an excipient is not seen. The instant application has not provided a definition for either of the terms. One of ordinary skill in the art knows that some substances can be used as both an excipient and a carrier. For this reason the compositions of instant claim 20 and that recited in claim 19 of the '897 patent are seen to overlap.

The obviousness-type double patenting rejection of instant claims 1-7 as being unpatentable over claims 19-20 of US Patent No. 6,441,022 has been rendered moot by cancellation of instant claims 1-7. The obviousness-type double patenting rejection of instant claim 20 as being unpatentable over claim 8 of US Patent No. 6,441,022 ('022 patent) is being maintained for reasons of record.

Instant claim 20 is drawn to a pharmaceutical composition comprising a carrier, the compound of formula I and the other active ingredient according to claim 9. Since the claim recites the open-ended language comprising, the said composition can comprise additional ingredients. Claim 8 of the '022 patent is also drawn to a composition comprising compounds of formula 1, which happens to substantially overlap with the compounds of instant formula 1 and also comprises an excipient. A clear-cut distinction between a carrier and an excipient is not

seen. The instant application has not provided a definition for either of the terms. One of ordinary skill in the art knows that some substances can be used as both an excipient and a carrier. For this reason the compositions of instant claim 20 and that recited in claim 9 of the '022 patent are seen to overlap.

The obviousness-type double patenting rejection of instant claims 1-7 as being unpatentable over claims 31-35 of copending Application No. 10/606,771 ('771 patent) has been rendered moot by cancellation of instant claims 1-7. The obviousness-type double patenting rejection of instant claim 20 as being unpatentable over claims 31-35 of copending Application No. 10/606,771 is being maintained for reasons of record.

Applicants have requested that this provisional rejection be held in abeyance until the claims of the '771 have been allowed.

Effective June 8, 1995, any continuing application of a previously filed application will expire twenty years from the filing date of the earlier case. A terminal disclaimer is still required to overcome a nonstatutory double patenting rejection in a continuing application, even though both patents would expire on the same day anyway because of the twenty-year term provisions under GATT/NAFTA. The reason is that the enforceability/common ownership provision of a terminal disclaimer under 37 CFR 1.321 (C)(3) remains. A terminal disclaimer includes a provision that the later filed application which matures into a patent shall only be enforceable as long as the earlier and later filed patents are commonly owned. If and when the patents cease to be commonly owned, the patent containing the terminal disclaimer does not expire, but it becomes unenforceable. This would avoid the problem of an alleged infringer being harassed by

two different parties with patents covering the same patentable invention (as defined in 37 CFR 1.601(n)).

A terminal disclaimer is additionally required because the enforceability/common ownership provision that the later filed application which matures into a patent shall only be enforceable as long as the earlier and later filed patents are commonly owned. If and when the patents cease to be commonly owned, the patent containing the terminal disclaimer does not expire, but it becomes unenforceable. This would avoid the problem of an alleged infringer being harassed by two different parties with patents covering the same patentable invention (as defined in 37 CFR 1.601(n)).

Applicants have to file a Terminal Disclaimer inorder to overcome this rejection.

Claim Rejections - 35 USC § 103

The rejection of claims 1-7 under 35 USC 103(a) has been rendered moot by cancellation of the claims.

Claims 9 and 21 are rejected under 35 U.S.C. 103(a) as being obvious over Frick et al (US 6221897) in combination with Castaner (Drugs of the Future, 2000, 25(7), 679-685).

Claim 9 is drawn to a composition comprising a compound of formula (I) and a second active agent selected from ezetimibe and Caromax. Claim 21 is drawn to a process of producing a composition comprising the composition of matter as in claim 9 comprising mixing the compound of formula I and the other active ingredient of the composition with a pharmaceutically suitable carrier and converting the mixture into a form suitable for administration.

Fricke et al (US 6221897) disclose composition comprising benzothiepine 1,1-dioxide derivatives of formula I in which R^1 is butyl, ethyl; R^2 is OH; R^3 is a saccharide residue; R^4 and R^5 are methyl and Z is –(C=O)-C0-C6-alkyl-NH- (see col. 23, lines 1-67; col. 25, line 57 through col. 26, line 2). The composition disclosed by Fricke et al has other pharmaceutically active compounds including, in particular, one or more statins as another active ingredient (see col. 3, lines 1-18 and 45-47). The compositions are made by uniform and homogeneous mixing of the active compound with a liquid and/or finely divided solid excipient and additional constituents (see col. 4, lines 9-20). However, Frick et al do not teach the preparation of a composition wherein the other ingredient is ezetimibe or Caromax.

Castaner, drawn to hypolipidemic cholesterol absorption inhibitor, teach that ezetimibe is a potent cholesterol absorption inhibitor. It is very potent in inhibiting increases in plasma cholesterol (page 682, right column, line 10 through page 683, left column, line 13; page 684, right column, see paragraph starting under subtitle-Clinical Studies).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising the compound of formula (I) and another active agent like ezetimibe or Caromax to make a composition comprising both the active ingredients and a carrier since the said active agents and general process steps for making the same is seen to be taught in the prior art. One of ordinary skill in the art can recognize that a composition can be made in a suitable form for administration by mixing different active ingredients. The skilled artisan would be motivated to do so since the prior art process of making the composition by mixing the respective active ingredients is a simple and efficient process.

It is obvious to combine individual compounds taught to have the same utility to form a new composition comprising them for the very same purpose (In re Kerkhoven, 626 F. 2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980)).

Claims 1-3, 6-8 are rejected under 35 U.S.C. 103(a) as being obvious over Frick et al (US 6221897) in combination with Castaner (Drugs of the Future, 2000, 25(7), 679-685) has been rendered moot by cancellation of the claims.

Claims 9 and 20 are rejected under 35 U.S.C. 103(a) as being obvious over Frick et al (US 6221897) in combination with Castaner (Drugs of the Future, 2000, 25(7), 679-685) is being maintained for reasons of record.

Claim 9 is drawn to a composition comprising a compound of formula (I) and a second active agent selected from ezetimibe and Caromax. Claim 20 is drawn to a pharmaceutical composition comprising a carrier, an effective amount of compound of formula (I) and an effective amount of the second active agent such that the combination results in an effective amount of the composition of matter being effective.

Fricke et al disclose composition comprising benzothiepine 1,1-dioxide derivatives of formula I in which R^1 is butyl, ethyl; R^2 is OH; R^3 is a saccharide residue; R^4 and R^5 are methyl and Z is –(C=O)-C0-C6-alkyl-NH- (see col. 23, lines 1-67; col. 25, line 57 through col. 26, line 2). The compound of formula (I) and their pharmaceutically tolerable salts and physiologically functional derivatives are ideal pharmaceuticals for treating hyperlipidemia and also lowering serum cholesterol level (col. 3, lines 1-13). The composition disclosed by Fricke et al has other pharmaceutically active compounds as another active ingredient (see col. 3, lines 1-18 and 45-

47). Fricke also teaches effective dosage amounts of the compounds of formula (I) (col. 3, lines 20-30).

However, Fricke et al do not teach a composition comprising the compound of formula (I) and a cholesterol absorption inhibitor chosen from ezetimibe or Caromax as the other active ingredient.

Castaner, drawn to hypolipidemic cholesterol absorption inhibitor, teach that ezetimibe is a potent cholesterol absorption inhibitor. It is very potent in inhibiting increases in plasma cholesterol (page 682, right column, line 10 through page 683, left column, line 13; page 684, right column, see paragraph starting under subtitle-Clinical Studies).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising the compound of formula (I) and another active agent like ezetimibe to make a third composition comprising both the active ingredients in individually effective amounts such that the combination results in an amount of the composition that is also pharmaceutically effective, since the both the active ingredients and their effective dosage is seen to be taught individually in the prior art of record. It is well within the purview of one of ordinary skill in the art to determine and adjust the effective amounts of the active agents based on the dosage disclosed in the prior art.

It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose (In re Kerkhoven, 626 F. 2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980)).

It is respectfully pointed out that for the rejections of claims 1-7 and 21 and claims 1-3, 6-8 and 20 applicants have argued that the references cited do not render the claims obvious since

the references either alone or in combination do not teach or suggest a synergic effect as demonstrated in the data shown on page 18 of the instant application. Since claims 1-8 have been cancelled this argument is seen as being advanced for the rejections of claims 20 and 21.

Claims 20 and 21 are drawn to a pharmaceutical composition comprising compounds of instant formula (I), a carrier and a second active agent and the process for making such a composition. A pharmaceutical composition or a process for making it as instantly claimed need not necessarily be rendered unobvious because a synergistic effect is not suggested or obvious in the prior art. Synergism is important when it comes to treating a disease or a condition using the said composition wherein the synergistic effect of the active agents in combination in the treatment of a particular disease may not be obvious.

Claims 10-15 and 18-19 are rejected under 35 U.S.C. 103(a) as being obvious over Frick et al (US 6221897) in combination with AHFS Drug Information 1994, pages 1096-1102 has been overcome by applicants showing of a synergistic effect for the said methods of treatment.

Conclusion

1. Claims 9, 16, 17, 20 and 21 are rejected

2. Claims 10-15 and 18-19, drawn to treatment of specific disorders/conditions using the composition as instantly claimed, wherein the active agents of the composition have a synergistic effect is not fairly taught or suggested by the prior art of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GK

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